REMARKS

Claims 1-34 are pending, and claims 35-49 are canceled. Claims 23-34 are withdrawn by the Examiner according to the Restriction Requirement made final in the Office Action. Claims 1-22 are examined.

Support for Amendments

Claim 1 is amended to correct a typographical error in the listing of the amide bond group by inclusion of the hydrogen for proper valency of the nitrogen, and to reword the proviso according to USPTO practice. Support for the reworded proviso can be found in the structures on page 1 of the specification as filed, where the excluded compounds 1 and 4 are presented.

Claims 3-6, 8-9, and 18-20 are amended to remove non-elected subject matter, as required on page 8 of the Office Action.

Claim 10 is amended to reword the definition of R according to USPTO practice. Support for the amendment can be found in the definition of R in claim 1 from which claim 10 depends, and in the previous wording of claim 10 where R is not H.

No new matter is entered.

Objection

The Office Action objects to claims 3-6, 8-9, and 18-20 "for containing non-elected invention" (Office Action, page 8, lines 17-18). By amendment, claims 3-6, 8-9, and 18-20 are directed to the elected invention, as required by the Office Action.

Rejection Under 35 U.S.C. § 112, 2nd paragraph

The Office Action rejects claims 1-22 under 35 U.S.C. § 112, 2nd paragraph, as being indefinite for the same reasons as for the lack of enablement rejection (see Office Action, page 6). Applicants request clarification as to how the claims are indefinite. With respect to the "wiggle lines" as discussed in the Office Action, the Examiner is referred to the standard conventions of chemistry according to IUPAC. A copy of basic terminology is cited in the attached Information Disclosure Statement.

In addition, the Office Action rejects claim 10 for failing to recite the definition of R. By amendment, claim 10 recites the definition of R.

Applicants respectfully request withdrawal of the rejection.

Rejection Under 35 U.S.C. § 112, 1st Paragraph

The Office Action rejects claims 1-4, 7-8, 10-12, 15-18, and 21-22 under 35 U.S.C. § 112, 1st paragraph, for failing to comply with the written description requirement. The Office Action argues that "the wiggle lines in the compound imply it is not stereo-specific," (Office Action, page 3) and that there is insufficient support because the "invention is directed to making both isomers at position 6 only" (Office Action, page 3). Finally, the Office Action rejects the incorporation of a US patent in claim 1.

By amendment, the proviso in claim 1 is reworded according to USPTO practice to remove the reference to a US patent. With respect to the "wiggle lines" or wavy lines according to IUPAC, these refer to the stereochemistry of the compounds rather than the stereo-specificity of their synthesis. Please find attached a copy of "Basic Terminology of Stereochemistry (IUPAC Recommendations 1996), also available at

http://www.iupac.org/publications/pac/ 1996/pdf/6812x2193.pdf. This document defines the meaning of a wavy line:

> A wavy line can be used to indicate either that the stereochemistry is unknown (**7**), but only one form is present, or if explained in the text, that both isomers are present and will be defined when required.

(see page 2196, paragraph 5). The instant specification states:

> The compound of the present invention represented by the above described formula **I** may include enantiomers depending on their asymmetry or diastereoisomers. Single isomers and mixtures or isomers fall within the scope of the present invention.

(page 8, paragraph 2). Furthermore, the specification contains a number of preferred embodiments wherein the stereochemistry is further defined, i.e. pages 8 to 11. Therefore, the disclosure in the specification clearly discloses that formula I includes stereoisomers and mixtures of stereoisomers.

The Office Action rejects claims 1-23 under 35 U.S.C. § 112, 1st paragraph, for lack of enablement for making and using the compounds as claimed. As claim 23 was withdrawn by the Examiner, Applicants understand the rejection to be directed to claims 1-22.

On page 4, the Office Action argues that the "specification fails to provide conclusive evidence that schemes 1 and 2 are applicable to making the recited groups" and the Office Action argues that steric hindrance will be a factor. In addition, the Office Action also argues that the specification fails to teach a method of making the racemate for claims 1-4, 7-8, 10-12, 15-18, and 21-22.

Evidence that the synthetic process disclosed in the specification is robust can be found in the variety of compounds made. Applicants direct the Examiner's attention to the variety of compounds in the Examples- see page 29-105 of the application as filed for complete

details of the synthetic schemes. With regard to steric hindrance, in making the compounds listed from pages 29-105, Applicants found no evidence of steric hindrance being the type of problem as suggested by the Examiner. Applicants note that the Office Action provides no support from the technical literature to suggest that steric hindrance is a problem with these compounds. Simply put, it is not clear how the Office Action arrives at steric hindrance as being a problem to warrant a rejection for lack of enablement.

The Office Action states that the specification fails to set forth how the schemes can be modified to make the racemate of position 6 (see Office Action, page 5). However, the Office Action itself provides an answer by stating that a racemic mixture can be obtained by adding together equal amounts of enantiomers. Applicants request clarification as to the Examiner's reasoning that this would not be a synthetic method, because in fact, this would be a synthetic method. In any event, short of mixing together enantiomers to achieve a racemic mixture, it is well known in the art how to use chiral auxiliaries as described in Schemes I and II, using reactions known as the Evan's aldol reaction. The specification discloses the synthesis of compounds 10a and 22. Each stereoisomer was obtained from compound 8a by Evans' aldol reaction with enantiomeric oxazolidinones 9 and 21. It is readily apparent to anyone in the field of organic chemistry that the use of an achiral oxazolidinone instead of the chiral auxiliary will provide a compound with racemic stereochemistry position position 6. In other words, removing the iPr group from the chiral auxiliary would result in a racemic synthetic scheme at position 6. Alternatively, it is quite apparent that using an equal mixture of chiral oxazolidinones 9 and 21 (rather than one or the other) would also result in a mixture at position 6. It is a well-established principle of patent law that it is not necessary, and even preferable to omit, that which is known in the art. As such, it is not necessary for the purposes of enablement to include basic concepts of

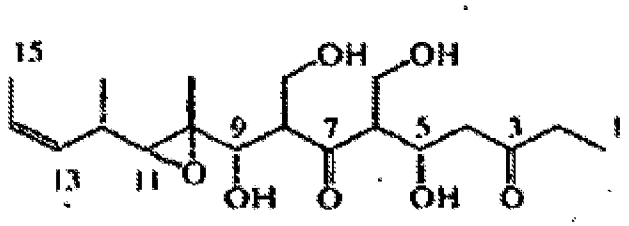
organic synthesis in the present application, as one of ordinary skill in the art (i.e. the synthetic organic chemist with graduate level training) does not need such teachings to practice the instant invention in making a racemate at a particular chiral center.

The Office Action further argues that once made, the compounds are not enabled to be used because the specification fails to provide evidence that the compounds would have the asserted utility. Applicants respectfully traverse, and direct the Examiner's attention to pages 106-112, where detailed results are presented for performing bioassays with the compounds. It is well known in the art of drug development to test compounds for biological activity. Applicants note that the MPEP specifically states that Office personnel should not impose on applicants the unnecessary burden of providing evidence from human clinical trials (see MPEP 2107.3 IV).

For the reaons above, and in view of the fact that the Office Action fails to consider the level of skill of one of ordinary skill in the arts (i.e., a synthetic organic chemists and medicinal chemists), Applicants respectfully request withdrawal of the rejection.

Rejection Under 35 U.S.C. § 102(b)

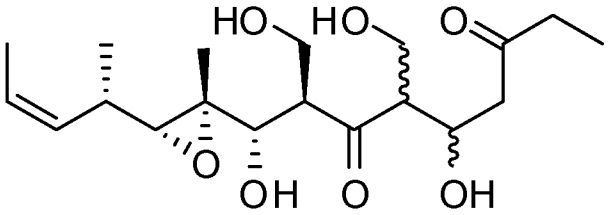
The Office Action rejects claims 1-6 and 22 under 35 U.S.C. § 102(b) as being anticipated by Zheng et al. (Chem. Pharm. Bull. (2000), vol. 48, issue 11, pages 1761-1765). The Office Action cites compound 4(1) of Zheng. Compound 4(1) of Zheng is as follows:



Myriaporone 4 (1)

(structure cut-and-pasted from Zheng, page 1761). Applicants note that Zheng names the compound as "Myriaporone 4" and uses "**1**" as a shorthand to identify the structural drawing in the text of the reference. Applicants further note that Zheng does not synthesize or isolate Myriaporone 4 himself, but rather describes synthetic approaches to a fragment of the compound. As noted by Zheng (and also as noted on page 1 of the instant specification), Myriaporone 4 as referred to by Zheng was first described by Rinehart et al. (US 5,514,708 and J. Nat. Prod., 1995, 58, 344).

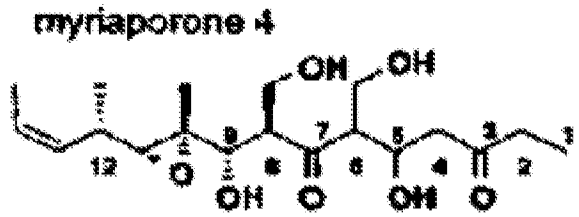
Applicants traverse the rejection on the basis that Myriaporone 4 is excluded from the instant claims by the proviso at the end of claim 1, which excludes the following structure:



The structure of the proviso encompasses compound 4(1) of Zheng, (also known as Myriaporone 4), as discussed on page 1 of the instant specification. The drawing of Zheng is regrettably blurry, but Myriaporone 4 (**1**) as disclosed by Zheng is encompassed by the proviso at the end of claim 1. Therefore, the claims are not anticipated.

Rejection Under 35 U.S.C. § 103(a)

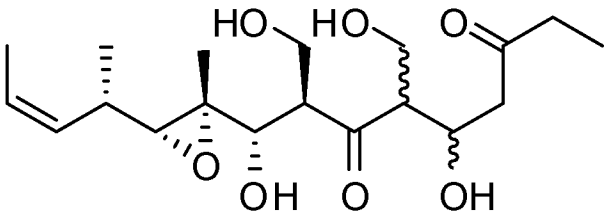
The Office Action rejects claims 1-22 under 35 U.S.C. § 103(a) as being unpatentable over each of the individual references: Zheng (cited above), Taylor et al. (Tetrahedron Letters, 1998, vol. 39, pages 9361-9364), and Rinehart et al. (U.S. Patent 5,514,708). Applicants note that all three references refer to the same compound: Myriaporone 4, which was first described by Rinehart, and then later referenced by Zheng and Taylor. The Office Action refers to a racemate at position 6. This is perhaps best illustrated by Taylor's drawing of Myriaporone 4:



(see Taylor, page 9361). The Office Action states that

> [t]he difference between the instant invention and that of the prior arts is that applicant claims both racemate and isomers instead of racemate by the prior arts. Also, applicant claims the compounds with known OH protecting groups.

(see Office Action, page 7). Applicants respectfully traverse the Office Action's characterization of the instant claims and the prior art. Applicants note that Myriaporone 4 is excluded from the instant claims by the proviso at the end of claim 1, which excludes the following structure:



The structure of the proviso encompasses Myriaporone 4, whether it is referred to as compound 4(1) of Zheng, Myriaporone 4 of Taylor, or Compound 4 of Rinehart.

With regard to compounds that are not Myriaporone 4, the Office Action argues that "[i]somer is not patentable over another isomer or racemate absent a showing of new and unexpected properties" with citation to *In re Brenner*, 147 USPQ 87, 247 F.Supp 51, 56 (DDC, 1965) (see Office Action, page 7). Applicants note that the cited decision actually states that "an optically active isomer is unpatentable over either the isomer of opposite rotation or, as in this case, the racemic compound itself," (*ibid.* at 56). Optically active isomers are properly referred to as enantiomers, and are configured in space to be mirror images of each other. Applicants note that the present claims encompass a variety of chiral centers such that compounds within the scope of the claims would have a diastereomeric relationship, and are not properly addressed by *Brenner*. In addition, it is noted that none of the cited references accomplish a synthesis of Myriaporone 4. On the contrary, Rinehart isolated the Myriaporone 4 from its natural source, while Zheng and Taylor each attempted synthetic studies towards Myriaporone 4, but were unable to achieve its synthesis. Therefore, even the enantiomer of Myriaporone 4 with opposite rotation, which would be expected to have similar physical properties but not necessarily similar biological properties, was unavailable to Rinehart, Zheng, and Taylor.

It is a well-established principle of patent law that "[I]f the prior art of record fails to disclose or render obvious a method for making a claimed compound, at the time the invention was made, it may not be legally concluded that the compound itself is in the possession of the public. In this context, we say that the absence of a known or obvious process for making the claimed compounds overcomes a presumption that the compounds are obvious, based on the close relationships between their structures and those of prior art compounds." *In re Hoeksema*, 399 F.2d 269, 274-75, 158 USPQ 597, 601 (CCPA 1968). The courts have also held that "[T]he presence or absence of a suitably operative, obvious process for making a composition of matter

may have an ultimate bearing on whether that composition is obvious-or nonobvious-under 35 U.S.C. 103." *In re Maloney*, 411 F.2d 1321, 1323, 162 USPQ 98, 100 (CCPA 1969). See also MPEP 2144.09 IV. The Office Action improperly uses Applicants' own disclosure in hind-sight reconstruction of a method of synthesizing the claimed compounds to render the claimed compounds obvious.

In addition to the problem of the prior art failing to teach a synthesis of Myriaporone 4, the prior art fails to provide motivation to add protecting groups to Myriaporone 4. The Office Action argues that one of ordinary skill in the art would have known to add OH protecting groups at the time the instant invention was made. On the contrary, it does not stand to reason that one would add protecting groups to a finished product. As is known in the art, protecting groups are used in the synthesis of a compound to achieve a transformation in one location of a compound while leaving another part unchanged. However, as the compound Myriaporone 4 as described in Rinehart, Zheng, and Taylor was only available through isolation as a natural product rather than through synthesis, one of ordinary skill in the art would have no reason to add a protecting group to it because it was already the finished product.

The disclosure of the present invention is concerned with new antitumoral compounds, which are available by a novel synthetic route. The derivatization described in the instant application also leads to a wide range of compounds for which biological activity data are presented at pages 106-112 of the application as filed. The data presented in the prior art neither teaches nor contemplates the range of compounds now shown to be biologically active. Simply put, the prior art cited in the Office Action fails to provide access or motivation to achieve the presently claimed compounds. Therefore, Applicants respectfully request withdrawal of the rejection.

AUTHORIZATION

The Commissioner is hereby authorized to charge any additional fees which may be required for consideration of this Amendment to Deposit Account No. **50-3732**, Order No. 13566.105013. In the event that an extension of time is required, or which may be required in addition to that requested in a petition for an extension of time, the Commissioner is requested to grant a petition for that extension of time which is required to make this response timely and is hereby authorized to charge any fee for such an extension of time or credit any overpayment for an extension of time to Deposit Account No. **50-3732**, Order No. 13566.105013.

Respectfully submitted,
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Dated: March 27, 2008

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